NICE National Institute for Health and Care Excellence

Implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx insertable cardiac monitor and Reveal LINQ Insertable Cardiac Monitoring System) to detect atrial fibrillation after cryptogenic stroke

Diagnostics Assessment Report (DAR) - Comments

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Biotronik	1	Entire report	Entire report	It is acknowledged that the DAP methods manual endorses the concept of diagnostic test accuracy, which is an aggregate of variable disease epidemiology in a given population and non-variable diagnostic test characteristics such as sensitivity and specificity. However, the report makes little effort to clearly differentiate diagnostic accuracy parameters which are dependent on the CS population from those independent from it. Parameters likely to vary between populations are anything tied to the prevalence or incidence of AF in a given population (detection rate in a certain time frame, PPV, NPV, etc), which is acknowledged appropriately by the evaluators in their report. Sensitivity and specificity, on the other hand, are independent of the population of interest subjected to the test.[1] In other words a diagnostic technology with 100% sensitivity can correctly identify all patients with the disease regardless of the population. As a result, the clinical evaluation presents several data generated in non-CS patients as unsuited or highly uncertain where there is no rationale to do so. In contrast, the economic evaluation (based on clinical advisor guidance) states *"… that there would not be any substantial differences in detection rates for the devices. As such, the EAG has assumed equal efficacy for all devices*." (page 86).	Applicability of sensitivity and specificity values for ICMs in non-CS populations to a CS population is unproven. As such, the clinical effectiveness results should be interpreted with caution. Assumptions have been made in the economic model to enable a comparison of the ICMs based on clinical expert advice and the results and conclusions are caveated to highlight their uncertainty.

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				The clinical section and the report summaries should be worded more accurately in regards to data informing on parameters unrelated to disease epidemiology or other characteristics of CS population. Reference: 1 Lalkhen, A. G., & McCluskey, A. (2008). Clinical tests: sensitivity and specificity. Continuing Education in Anaesthesia Critical Care & Pain, 8(6), 221-223.	
Biotronik	2	iv	Abstract (Objectives)	*"To assess the diagnostic test accuracy (DTA), and clinical and cost-effectiveness of BioMonitor 2-AF, Confirm RX, and Reveal LINQ for detecting AF after 24 hours of external ECG monitoring in CS patients."* Such description of the objective does not align with the previously released final scope and protocol which state ➢ "*Does the use of implantable cardiac monitors to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke represent a cost effective use of NHS resources?"* (final scope), and ➢ "*The aim of this diagnostic assessment review is to assess whether the use of implantable cardiac monitors to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke represents a cost-effective use of National Health Service (NHS) resources compared to no further testing after outpatient*	No change required. The word limit for the abstract prohibits a comprehensive description of the review objectives.

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				external ambulatory electrocardiogram (ECG) monitoring" (final protocol), respectively. • The statements in the final scope and protocol define the primary decision problem as to compare a treatment strategy (ICM) with the standard of care (24 hours ECG followed by no further testing) for its cost-effectiveness. The report statement in question does not mention this primary objective at all. The reason for the deviation is unclear. • **The sentence should be re-worked as follows: *"To assess the diagnostic test accuracy (DTA), and clinical and cost-effectiveness of ICMs for detecting AF after 24 hours of external ECG monitoring in CS patients."* and the inter-device comparisons be given less emphasis here.**	
Biotronik	3	v	Abstract (Results)	*"However, BioMonitor 2-AF and Confirm RX could only be included in the analysis by making a strong assumption of equivalence with Reveal LINQ.".* • The statement is misleading. Device accuracy data (sensitivity and specificity), which are unrelated to disease epidemiology (see comment no 1), was available for each equivalent device. Data provided in the CRYSTAL-AF are the prevalence and incidence for AF in CS population. • Since the investigated devices all show the capability of detecting AF, they are all definitely justifiable to be included in the analysis. The strong assumption should be made is the CRYSTAL-AF actually	As no data on detection rates in a CS population are available for BioMonitor AF-2 and Confirm RX, using data for another manufacturer's device (Reveal XT) and assuming equivalence, from a methodological standpoint, is a strong assumption. Therefore, no change is required in the report.

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				presents the true AF prevalence and incidence since there is no accepted gold standard for evaluating AF and using imperfect diagnostic tests as the benchmark can lead to substantial error in the estimation of necessary prevalence and incidence of the AF in CS population for this DAR.[2] • **The sentence should be either deleted or rephrased.** Reference: 2. Cipriano, L. E., & Sposato, L. A. (2016). Estimating the sensitivity of holter to detect atrial fibrillation after stroke or transient ischemic attack without a gold standard is challenging. American Journal of Cardiology, 117(2), 314-316.	
Biotronik	4	v	Abstract (Conclusions)	"*The evidence suggests that the Reveal LINQ is more effective in detecting AF than SoC but there is insufficient clinical data in a CS population to draw conclusions for the Confirm RX and BioMonitor 2-AF. The cost-effectiveness results indicate that ICMs could be considered a cost-effective use of NHS resources compared with SoC for patients who have had a CS and no AF has been detected after 24 hours of external ECG monitoring*." • See comment number 1. • See comment number 2. This conclusion does not answer the primary decision problem. • **The statement should be rephrased as:**	No change required. Please see responses to comment no. 1 and 2 for further details.

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				"The evidence suggests that the ICM is more effective in detecting AF than SoC. The cost-effectiveness results indicate that ICMs could be considered a cost-effective use of NHS resources compared with SoC for patients who have had a CS and no AF has been detected after 24 hours of external ECG monitoring."	
Biotronik	5	xviii	Results	*"The results of the mixed population studies suggest that enhancements over time to the AF diagnosis algorithm in the Reveal ICMs has improved their DTA. A naïve comparison of the mixed population DTA studies of the Confirm DM2102 and Reveal LINQ suggests they both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively)."* • The sentence provides the impression that the 100% sensitivity data for LINQ were derived from studies with actual CS patients, but the analysis on LINQ's performance (Puererfellner et al 2018) was based on the bench test simulations with incorporated ECG data from the previous studies in a mixed population. • **The origin of the LINQ test accuracy data should be stated more clearly**.	No change required. The sentences highlighted by the company both clearly state that the origins of the data are from mixed population studies.
Biotronik	6	xviii	Summary of clinical effectiveness results	*"… both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively). …. However, this comparison is subject to clinical heterogeneity (patient populations, interventions and study designs) and the data are not necessarily reflective of CS patients or the ICM models of interest.*	No change required. Please see response to comment no. 1 for further details.

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				• As mentioned in comment no 1, sensitivity and specificity are unrelated to population characteristics but particular for a given diagnostic method (here a device algorithm). Each device will detect with the same sensitivity and specificity regardless of in which population it is used. • **The last sentence of this paragraph should be deleted.**	
Biotronik	7	xix	Summary of cost-effectiveness results	*"However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the CS population and as such there is substantial uncertainty in the results."* • Data were provided that describe both specificity and sensitivity of the BioMonitor 2-AF for detecting various cardiac arrhythmia including AF. These data are unlikely to vary between populations. See comment no 1. • The main assumption made in regards to the C/E assessment of these two device models were on the AF prevalence in a CS population. There is far less uncertainty than indicated here. • **The sentence should be worded less restrictive.**	As per response to comment 3. No change required in the report.
Biotronik	8	xx	Clinical discussion	*"There is also evidence to suggest that AF detection in ICM devices, is dependent on various factors including the patient population and incidence rate of AF, thus limiting the use of data in non-CS populations to draw meaningful conclusions."*	As per response to comment 1. No change required in the report.

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				• There is no acknowledgement that some elements of 'AF detection' can indeed be inferred from one population to another, so non-CS data are relevant too and were available for this evaluation. • **The statement should appreciate this and be modified as follows:** **"While AF detection rate in ICM devices is dependent on various factors including the patient population and incidence rate of AF, data in non-CS populations were appropriate to inform on test sensitivity and specificity.".**	
Biotronik	9	xx	Scientific summary	*"Nevertheless, they suggest the newer models of the ICMs (e.g. Reveal LINQ and Confirm RX) are easier to insert, associated with fewer AEs and suitable for insertion by trained nurses and cardiac physiologists."* • The statement ignores evidence submitted for the BioMonitor 2-AF showing the ease of insertion. In addition, the definition of "newer models" of ICMs is too unspecific and could be misleading. All miniaturized devices (including the BioMonitor 2-AF) are easier to implant than previous more bulky device generations. • **The sentence should be rephrased as follows: "…newer miniaturized models of the ICMs are easier to insert, associated with fewer AEs and suitable for insertion by trained nurses and cardiac physiologists."**	No change required in the report. Two devices are named only as an example.

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Biotronik	10	xx	Cost-effectiveness discussion; other instances in the report referring to 'incidental findings'	*"…However, data on incidental findings …"* • The term 'incidental findings' might be misleading. ICMs are indicated to detect cardiac arrhythmias, AF being one amongst others. The diagnostic work up tends to focus on AF because of its potentially serious implications but the overarching goal of ICM insertion is to detect any cardiac rhythm anomaly and to channel patients into various treatments (e.g. IPG for asystole or bradycardia, ICD for high ventricular rates). • **The wording in the report should not relegate such other important diagnostic results to 'incidental findings'.**	NICE and the specialist committee consider the use of the term incidental findings to refer to cardiac arrythmias other than AF detected in CS patients fitted with an ICM. No change required in the report.
Biotronik	11	xxi	Scientific summary	*"The evidence suggests that the Reveal LINQ is more effective in detecting AF than conventional follow-up and is associated with low AE rates. However, there is insufficient clinical data available for the Confirm RX and BioMonitor 2-AF in a CS population and so it is not possible to draw conclusions on their clinical efficacy or how any of the ICMs might compare with each other.* • See comment number 1 and 4. • **"The evidence suggests that the ICMs are more effective in detecting AF than SoC and associated with low AE rates. Although there are studies showing the sensitivity and specificity of the investigated ICMs in detecting AF, a strong assumption is made to assume the**	As per previous responses, no change required in the report.

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				prevalence of AF in CS population can be based on the data obtained from CRYSTAL-AF."	
Biotronik	12	xxi	Conclusions	*"The evidence suggests that the Reveal LINQ is more effective in detecting AF than conventional follow-up and is associated with low AE rates. However, there is insufficient clinical data available for the Confirm RX and BioMonitor 2-AF in a CS population and so it is not possible to draw conclusions on their clinical efficacy or how any of the ICMs might compare with each other."* • See comment no 1 and 4 • **The statement should be rephrased and the statement concerning insufficient data in a CS population should be dropped: "The evidence suggests that ICMs are more effective in detecting AF than conventional follow-up and associated with low AE rates."**	As per previous responses, no change required in the report.
Biotronik	13	11	1.3.3	*"Clinical expert opinion and evidence from a mixed population suggest that the Reveal LINQ has better specificity than the XT (Section 3.4.3), is easier to implant and leads to fewer complications due to its size, and that AF detection accuracy between the devices is similar."* • **This statement is misplaced in a section that is to describe the technology ahead of the actual assessment, and thus, should be removed.**	No change required in the report. The text links to evidence presented in a later Section of the report and has been included to highlight the key differences between the Reveal LINQ and Reveal XT.

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Biotronik	14	22	3.1	*"As discussed above, there were no published or ongoing studies identified that assess the diagnostic accuracy of any of the three ICM devices exclusively in a CS population. However, this is not altogether unsurprising given that the incidence of AF is very low in the CS patient population and, therefore, a very large study with long-term follow-up consistent with the battery life of the ICM device would be required to have enough patients detected with AF on a short-term Holter monitor in order to assess the diagnostic test accuracy (DTA) of an ICM. As such, it is unsurprising that DTA data were not identified for any of the three ICMs under review in the CS population."* • The statement leaves the impression that there is no evidence at all on the different components of diagnostic accuracy for any of the three devices, which is not true. • See comment 1 and 3. • **The statement should make reference to not all parameters of 'diagnostic accuracy' having to be generated in CS patients.**	As per response to comment 1. No change required in the report.
Biotronik	15	60	3.4.2	*"In summary, the studies of the BioMonitor 2 suggest that it is clinically effective in detecting AF and is associated with low levels of AEs and reasonably good levels of patient satisfaction. However, it should be noted that these results are not exclusively for the BioMonitor 2-AF or a CS population and therefore should be interpreted with caution."*	As per response to comment 1. No change required in the report.

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				• The performance parameters specificity and sensitivity of the BioMonitor 2-AF are unaffected by in which population the device is used. • See comment Number 1 • **The reference to the CS population should be deleted.**	
Biotronik	16	61	3.4.3 Table 23	It is not clearly visible from the table that two of the reported data sets were actual patient studies (Hindricks 2010, Sanders 2016), whereas the other two studies (Puerefellner 2014 and 2018) were bench test simulations based on re-using ECG data from the former mentioned two patient cohorts. • **The table should be improved so the difference in the approach and the re-use of previous dataset is easier to comprehend.**	No change required in the report. The studies are clearly described in the text and the column headings of the table state which data are described in each column.
Biotronik	17	67	3.5.2	*"…the newer models of the ICM's (e.g. Reveal LINQ and Confirm RX) were easier to insert and were suitable for insertion by trained nurses and …"* • See comment number 9 • **The sentence should be rephrased as follows: "…newer miniaturized models of the ICMs were easier to insert…"**	As per response to comment 9. No change required in the report.
Biotronik	18	67	3.5.1	*"However, company submissions and the EAG's clinical experts reported that the newer models of the ICM's (e.g. Reveal LINQ and Confirm RX) were easier to insert…."* • See comments number 9 • **The sentence should be rephrased as follows:**	As per response to comment 9. No change required in the report.

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				"…newer miniaturized models of the ICMs were easier to insert…"	
Biotronik	19	101	5.1.1	*"Table 40 presents the fully incremental analysis of cost-effectiveness results and demonstrates that out of the ICMs under consideration, Reveal LINQ is dominated by BioMonitor 2-AF. However, BioMonitor 2-AF would not be considered cost-effective when compared with standard of care (SoC) monitoring."* • This conclusion is caused by a mistake in table 40 and in contrast to other instances in the report. See also figure 9 which identifies the BioMonitor 2-AF as dominant treatment option when compared to the SoC. • **The sentence should be replaced as follows: "Table 40 presents the fully incremental analysis of cost-effectiveness results and demonstrates that out of the ICMs under consideration, both Reveal LINQ and Confirm RX are dominated by BioMonitor 2-AF."**	Thank you for highlighting this error, this has been changed and can be found in the erratum document accompanying the EAG report.
Biotronik	20	101	Table 40	The device labels / data for the BioMonitor and Confirm RX are mixed up. • **The device names in the table need to be swapped.**	Thank you for highlighting this error, this has been changed and can be found in the erratum document accompanying the EAG report.
Biotronik	21	101	5.1.1	*"However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the cryptogenic stroke (CS) population and as such they are based on a strong*	As per response to comment 3. No change required in the report

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				assumption of equivalence with Reveal LINQ, which are not proven." • See comments 1 and 3 • **This sentence should be deleted.**	
Biotronik	22	121	6.1.1	*"However, company submissions and the EAG's clinical experts reported that the newer models of the ICMs (e.g. Reveal LINQ and Confirm RX) were easier to insert and were suitable for insertion by trained nurses and cardiac physiologists."* • Please see comments number 9 • **The sentence should be rephrased as follows: "…newer miniaturized models of the ICMs were easier to insert…"**	As per response to comment 9. No change required in the report.
Biotronik	23	121	6.1.2	*"No data were obtained for BioMonitor 2-AF or Confirm RX. As such, a strong assumption was made in the economic analysis, based on clinical expert opinion, that the effectiveness of ICMs are similar and thus the detection rates obtained from CRYSTAL-AF were used … "* • The term detection rate might be misleading here. CRYSTAL-AF informs on the AF prevalence in a CS population but not on the test accuracy of any of the evaluated ICM devices. Data on test accuracy (even though sometimes inferred from previous device generations) were available for all three ICMs, and clinical expert advisors deemed them *"at least as good as the rates seen in CRYSTAL-AF"* (page 126).	As per previous comments, no change required in the report.

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				• Also see comments 1 and 3. • **The sentence should be rephrased as "No detection rates of AF in the CS population were obtained for BioMonitor 2-AF, Confirm RX or Reveal LINQ, but studies showing the sensitivity and specificity of the investigated ICMs were obtained. The only one detection rate of AF in CS population was obtained from CRYSTAL-AF, which was based on Reveal XT—a predecessor of LINQ. As such, a strong assumption was made in the economic analysis, based on clinical expert opinion, that the effectiveness of investigated ICMs are similar and thus the detection rates obtained from CRYSTAL-AF were used … "**	
Biotronik	24	121	6.1.2	*"However, the results for BioMonitor 2-AF and Confirm RX should be viewed with caution, as no data were available for any version of these devices in the CS population and as such there is substantial uncertainty in the results."* • See comments 1 and 3 • **The sentence should be deleted.**	As per response to comments 1 and 3. No change required in the report.
British Cardiovascular Society	25			I would agree…that the premise that short lived episodes as they define it are significant when there is increasing evidence that episodes of AF lasting less than 12 hours are associated with very low risk. I would be much more inclined to look hard if the patient had no other explanation for stroke (no vascular disease etc,) and had a high risk of AF thank if they had hypertension or other stroke promoters. I worry that this will be promoted by the	No change required in the report.

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				company as a reason to implant loop recorders in all cryptogenic stroke.	
British Cardiovascular Society	26			The other thing that surprises me is that they have accepted a sensitivity of these devices as 100% when we know that this is not true and depends on the programming.	No change required in the report.
British Cardiovascular Society	27			They assume that someone with CS without AF on a 24 hour tape will see a cardiologist at 1,3,6 and 12 months. That sounds unlikely to me (not to say impossible, given my 5 month follow up clinic appointment waits at the moment)	This assumption was informed by clinical experts, but can be viewed as conservative, as it increases the cost of the SoC arm of the model. No change required in the report.
British Cardiovascular Society	28			Is 24 hours monitoring really the standard of care against which these devices should be measured? – I'd be requesting a longer 72 hour or even 7 day tape for someone who I thought might have had AF. isn't there a big leap in assuming that brief runs of asymptomatic AF identified on an implanted device carry the same risk of stroke as clinically diagnosed AF or PAF? Seems unlikely that someone who is 99%+ of the time in SR has the same stroke risk as someone who is 99%+ in AF. So the cost effectiveness of the devices in preventing stroke is unproven – correct?	No change required. The clinical and cost-effectiveness reviews are based on diagnosis of paroxysmal AF in line with clinical expert advice. A minimum of 24 hours external ECG monitoring was required based on clinical expert advice although studies of longer durations were also included.
British Cardiovascular Society	29			It's a really interesting and comprehensive analysis. I suspect that Standard of Care across the country for AF detection in cryptogenic stroke patients probably ranges	No change required in the report.

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				from nothing through various durations of Holter monitoring up to ILRs. I think they've gone for 24 Holter in the analysis as that is what the comparator was in the CRYSTAL AF study that underpins a lot of the clinical and economic evidence covered.	
British Cardiovascular Society	30			I think multiple reviews with a cardiologist at 1, 3 ,6 and 12 months in patients with CS and no AF is v unlikely to reflect routine clinical practice in many places in the UK.	As per response to comment 27, no change required in the report.
British Cardiovascular Society	31			The only other thing that struck me is that there is no mention of resource impact – this is likely to lead to considerable uptake in ILR implant rates. Following these devices up is not trivial – they can produce a lot of 'noise' which has to be assessed by a physiologist. We all know that there is a UK wide shortage of trained physiologists, so whether there is adequate resource available to implant and follow-up a large increase in ILRs for CS patients needs to be explored/acknowledged.	Implementation of devices if approved is outside the remit of the report. No change required.
British Cardiovascular Society	32			Although I agree with your comments (*ie comment 7*) that should not be a reason for patients not to receive appropriate treatments/monitors. Perhaps if they were approved this may lead to more trained physiologists to meet demand? I do not think we should highlight this shortfall of resources just focus on whether the device is suitable	No change required to the report.
Royal College of Physicians	33			We would like to endorse the response submitted by the British Cardiovascular Society.	No response required.

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Northern England Clinical Networks (Stroke)	34	88-89		The estimates of the risks of stroke and of the treatment effect of anticoagulants in reducing these risks are not appropriate for inclusion in the model. The paper quoted from Sterne et al is an analysis of the effects of anticoagulant treatments from an analysis of trials where patients predominantly or exclusively had persistent atrial fibrillation or at least prolonged periods of atrial fibrillation which could be captured on ECG. There has been no trial of the effect of anticoagulants on reducing the risk of stroke in patients with the brief episodes of atrial fibrillation picked up by the implantable monitors that your current appraisal addresses. There is good reason to believe that the effect of anticoagulants in patients with brief episodes of atrial fibrillation is much smaller than in the patients included in the anticoagulant trials, and there may well be no reduction in risk at all. Further, the baseline risks of stroke in the model are based on the CHADVASC risk scoring scheme, which is also based on patients with persistent or prolonged episodes of atrial fibrillation. There is good reason to believe that the risks of stroke in patients with briefer episodes of atrial fibrillation, such as those picked up by these technologies as opposed to current standard care, are considerably smaller. For episodes of atrial fibrillation at the shorter end of the range the risk is likely to be no	As per the NICE guideline (CG180) and clinical expert advice, if atrial fibrillation is diagnosed after a stroke, antiplatelet therapy should be discontinued, and anticoagulation should be initiated. All inputs in the model have been adjusted to reflect a secondary prevention stroke population with paroxysmal AF (the updated DOAC model based on Welton *et al.* 2017). No change required to the report.

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				higher than for patients without episodes of atrial fibrillation. The risks of adverse effects from the treatment are likely to apply to all patients treated however. As a result this analysis is almost certainly substantially overestimating clinical benefit, and it is quite likely that anticoagulant treatment in this group of patients generate harms that outweigh any benefit altogether. In conclusion the analysis is seriously flawed because there is no evidence of clinical effectiveness of the treatment considered in the patient group detected by these technologies. The conclusion that these technologies should be recommended based on this analysis is unwarranted and may well result in substantial harm to patients as well as unjustified financial costs.	
Abbott	35			We have no comments to make on the DAR for this assessment.	No response required.
Medtronic	36	General comment		We thank you for sharing the assessment report and the cost-effectiveness model and for the opportunity to comment. Overall the EAG has provided an excellent assessment. We believe it is problematic that the EAG has presented the results of a comparative economic model including	As per the NICE final scope, Reveal LINQ, BioMonitor AF-2 and Confirm RX were identified as devices required for comparative assessment. Clinical experts were consulted regarding the efficacy of the devices in lieu of AF detection data being available in the CS population for each of the

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				two devices without clinical evidence. As the EAG recognised, the diagnostic performance of an ICM in a known AF population cannot be applied to the CS population. While quantifying AF burden in patients with known, regular and comparatively long episodes is a foundational functionality of these devices, detecting new AF patients who have initially few and short episodes is much more challenging. The diagnostic performance measures will inevitably be better in patients who already have AF as they are strongly related to AF incidence and duration. CS patients in contrast are indicated for an ICM if AF was not diagnosed based on external cardiac monitoring and only a proportion of CS patients will be detected with AF after 3 years. Abbott and Biotronik devices differ from the Medtronic devices in many aspects, importantly, the underlying algorithm and programming options to detect AF are completely different. The results from the Crystal AF study can therefore not be transferred to those devices on the premise that the devices are capable of monitoring AF in a known AF patient population. We therefore suggest that the Abbott and Biotronik devices are removed from the economic analysis.	devices. However, it has been made clear that the cost-effectiveness results for BioMonitor AF-2 and Confirm RX are based on strong assumptions of AF detection equivalency and that the results carry substantial uncertainty as a result. No change to the report is required.
Medtronic	37	General comment		We have observed that the diagnostic yield from the Crystal AF Study is shown as 19% at 36 months in the report. While we recognise that reporting an intention-to	Thank you for highlighting this discrepancy, the text has been changed and the changes

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				treat estimate from an RCTs is generally the gold standard approach for evidence-based medicine, it may substantially underestimate diagnostic yield in studies with substantial loss to follow-up. In the Crystal AF study the secondary endpoint was 12 months follow up and only a small number of patients reached 36 months follow-up. In addition, the Kaplan Meier estimate reported in the Crystal AF study may be more informative as it takes account of both occurrence and timing of a particular event (similar to a survival analysis). It may help the NICE Committee to clarify that the 19% is the percentage of patients in the study that got a diagnosis by 36 months and not the probability of AF being diagnosed by 36 months (30%).	can be found in the erratum document accompanying the EAG report.
Medtronic	38	iv	Abstract	We recommend changing “risk of stroke recurrence can be reduced with AF treatment” to “a guideline recommended change in therapy to anticoagulation to reduce stroke recurrence” since anticoagulation is not in fact treating AF but simply reducing stroke risk as a result of AF.	No change required in the report. Anticoagulation is a part of the treatment pathway for AF and the word limits for the abstract prohibit extensive description.
Medtronic	39	v xix xxi	Abstract SCIENTIFIC SUMMARY SCIENTIFIC SUMMARY	“When each device is compared incrementally, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX” Since some of the NICE committee members will not be experienced in cost-effectiveness analysis, we believe it would be important for the EAG to more prominently explain that the dominance of BioMonitor 2-AF in the	No change in the report is required.

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		121 128	6.1.2 7.2	model is purely based on a price differential and that Confirm RX and BioMonitor 2-AF have no device specific evidence in the CS population. We recommend changing this to: "When each device is compared exclusively on price and longevity, BioMonitor 2-AF dominates Reveal LINQ and Confirm RX."	
Medtronic	40	xviii 65 119	SCIENTIFIC SUMMARY (Results) 3.5.2 6.1.1	"A naive comparison of the sensitivity and specificity data from non-CS or mixed populations in the studies flagged of relevance by the respective companies of the Confirm DM2102 (older model of Confirm RX) and Reveal LINQ suggests they both have 100% sensitivity for AF detection although specificity varies (85.7% and 99.0%, respectively). " We would suggest "AF detection" to be rephrased to "AF monitoring" mainly because the population involved in the quoted studies were known AF patients in whom the devices were used to quantify the burden of AF and not to detect infrequent occult AF.	No change required in the report. Sensitivity and specificity are measures of the effectiveness of the ICM devices in the detection of AF.
Medtronic	41	7	1.3 Table 2	We recommend a change to the description for Reveal LINQ in row "Detection and sensing parameters" as follows: "Atrial tachyarrhythmia (including Atrial Flutter/Atrial Fibrillation) (exclusive algorithm) P-wave	Thank you for highlighting this inaccuracy, the text has been changed and the changes can be found in the erratum document accompanying the EAG report.

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				morphology discriminator algorithm, bradyarrhythmia, ventricular tachyarrhythmia, pause episodes"	
Medtronic	42	7	1.3 Table 2	We suggest a change to the description for LINQ in the row "device storage" as follows: "14 months of daily time spend in AF (AF Burden), 27 minutes of automatic detected episodes, 2 min of the longest AF episode, 30 minutes of symptomatic episodes."	Thank you for highlighting this inaccuracy, the text has been changed and the changes can be found in the erratum document accompanying the EAG report.
Medtronic	43	12	1.3.3	For further clarity we suggest the addition of the following information after the sentence "Transmitted and stored data are encrypted": "CareAlerts can be setup on the CareLink website and are programmable without needing to bring patient in to the office. Notifications can be customized for email and SMS."	No change required in the report.
Medtronic	44	24	3.2.1	Concerning the paragraph on pre-enrolment screening for AF in Crystal AF, we believe it would be helpful to clarify that patients generally received either inpatient telemetry monitoring (extended Holter) or a traditional Holter. Based on the simulation study by Choe 2015 quoted in the assessment report, the yield of external cardiac monitoring is low in the CS population. Thus, the usefulness of performing a 24h Holter in addition to a median duration of 68h telemetry is doubtful. Finally, patient compliance to external monitors is a challenge, as	No change required in the report. Choe 2015 is a simulation study and there are no data presented to demonstrate a benefit of inpatient telemetry over outpatient Holter monitoring.

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				evident from the fact that most patients receiving a 24h Holter did not complete it.	
Medtronic	45	24	3.2.1	Factual Correction: In the paragraph above Table 3, only Table 3 should be referenced.	Thank you for highlighting this error, the text has been changed and the changes can be found in the erratum document accompanying the EAG report.
Medtronic	46	91	4.2.5 Table 30	We noticed that while the stroke management costs are weighted by severity of the stroke, the utility value for the health states are assumed to be the same. For consistency we recommend weighing the utility values by severity as well, or to recognize in the report that the current inputs make the calculations conservative.	No change in the report is required.
Medtronic	47	126	6.2.2	"Furthermore, the EAG's clinical experts advised that the detection rates for each of the devices will be at least as good as the rates seen in CRYSTAL AF." For additional clarity, we recommend rephrasing "the devices" to "the Reveal LINQ device"	The advice given by the clinical experts relates to all the devices under consideration. No change in the report is required.
Medtronic	48	127	7.1	We suggest the following addition to the first sentence of the last paragraph: The limited clinical data available for the Confirm RX and BioMonitor 2-AF suggest they both have good sensitivity and specificity "for monitoring AF in patients with known AF but" it is not possible to draw	No change required in the report.

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				conclusions how they perform in CS patients or how any of the devices compare with each other.	
Medtronic	49	Excel File	Model	It would be good to clarify whether the short-term (3-year) model includes recurrent stroke rates. Recurrent strokes did occur in the Crystal AF study and it thus would seem unrealistic not to include them in the first 3 years of the model. In addition, there were higher recurrent stroke rates in the SoC group in Crystal-AF (even though the difference was not statistically significant) and not modelling it would be a conservative assumption.	When patients are categorised into either “AF detected” or “AF-undetected” in each cycle during the 3-year short term model, they enter the long-term model where they are at risk of a second stroke as well as other events. However, the risks of these events are dependent on the treatment the patient is receiving (anticoagulation versus antiplatelet treatment). No change in the report is required.
Medtronic	50	Excel file	Model	On closer inspection of the economic model we have found a factual error regarding the cost input for the FOCUSON service and feel it is important to flag to you ahead of the committee meeting on the 16th April. There are two price options for FOCUSON. Hospitals can choose to pay for the service per year for a charge of £187 per patient or they can opt for a one-off fee per patient per device of £374. Costs for option 1 accrue to the hospital at the beginning of each year over the three years duration of the device. While the model has included the costs correctly in cycles 0, 4 and 8 – it has also included it in cycle 12. We kindly asked the EAG to remove the costs in cycle 12.	Thank you for pointing out the two errors. We have corrected them in the model and have sent an updated version to NICE. In addition, Table 41 and Figure 10 has been update and the changes can be found in the erratum document accompanying the EAG report.

Implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx insertable cardiac monitor and Reveal LINQ Insertable Cardiac Monitoring System) to detect atrial fibrillation after cryptogenic stroke

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				The costs for option 2 need to be assigned only in cycle 0 as the hospital pays the one-off fee at implant per patient per device. Currently, the FOCUSON costs are incorrectly assigned in every cycle. We kindly asked the EAG to remove the costs from all cycles except cycle 0. This of course would impact the reported ICERs for Reveal LINQ with the optional addition of FOCUSON on page 104 in Table 41 in the Assessment report.	